The Relationship Between a Genetic Variant in the HSPB1 Gene and a Lower Risk of Cardiovascular Diseases: The Results of the MASHAD Cohort Study

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Abstract- Coronary heart disease (CHD) is a leading cause of death, highlighting the importance of risk stratification and prognostic biomarkers in CHD. There is a growing body of evidence supporting the potential value of heat shock proteins (HSPs) in the pathogenesis of atherosclerosis. Here, we explored the relationship between serum anti-HSP27 levels and a genetic variant, rs2868371, in the HSPB1 gene in the Stroke and Heart Atherosclerotic Disorders (MASHAD) cohort study carried out in Mashhad. A total of 8776 subjects were recruited. Anti-HSP27 levels were measured using an in-house enzyme-linked immunosorbent assay (ELISA), followed by genotyping using a TaqMan® probe-based assay. Demographic, biochemical, and hematological characteristics of the population were evaluated in all subjects. Kaplan-Meier curves were utilized, while logistic regression models were used to evaluate the relationship between genotypic frequencies and clinical characteristics of the population. No significant difference in anti-HSP27 levels was demonstrated between subjects with and without CHD. The frequencies of the CC, CG, and GG genotypes were 68%, 26.8%, and 5.2%, respectively. CAD patients with GG and GC genotypes had a lower risk of myocardial infarction (MI) compared with the reference group after adjusting for confounding factors [OR=0.27 (95% CI=0.08-0.94), *P*=0.040]. Our data revealed a relationship between the genetic variant in the HSPB1 gene and the risk of developing CHD, supporting further research on the potential value of this emerging marker in predicting

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Introduction

Cardiovascular disease (CVD) is one of the leading causes of mortality worldwide (1). CVD includes coronary heart disease (CHD) and acute coronary syndrome (ACS). CHD comprises angina pectoris, myocardial infarction (MI), and silent myocardial ischemia (2). In other words, the prevalence of CVD is increasing worldwide, highlighting the need to identify novel prognostic biomarkers.

Cells are protected by heat shock proteins (HSPs) against various stresses, including high temperature, free radicals, shear stress, and toxins such as oxidized low-density lipoprotein cholesterol (LDL-C) (3). HSPs are involved in the pathogenesis of atherosclerosis (4). Although their role is not fully understood, serum concentrations of several anti-HSPs have been associated with the severity and progression of CVD (5). The expression of Hsp27, a member of the HSP family with a molecular weight of 27 kDa, is increased in cardiomyocytes in response to ischemia (6). Studies conducted over the past two decades have demonstrated a correlation between Hsp27 and CVD. Hsp27 is thought to play a critical role in the development of atherosclerosis (7). Recent studies have reported that Hsp27 expression is regulated by several stimulants involved in atherogenesis, including oxidative stress (8) , proteolytic activity, and inflammation. Serum Hsp27 titers appear to be a potential biomarker of cardiac ischemia (9).

Since no studies have investigated polymorphisms in the HSPB1 gene and their association with CVD worldwide or in the Iranian population, the purpose of the current study was to assess the association between the rs2868371 polymorphism and new coronary events among participants in the MASHAD study. The rs2868371 genetic polymorphism has been confirmed and sequenced in the 1000 Genomes Project and the Human Genome Project (HapMap Project). Moreover, this genetic locus, with a heterozygosity of 0.429 and a minor allele frequency of 0.3122, increases the efficiency of our study. This SNP is located in the 5′-near-gene region, and its functional role in the promoter region of the HSPB1 gene has been demonstrated (10) .

We therefore assessed the association between the presence of coronary artery disease (CAD) and the rs2868371 genetic variant in the HSPB1 gene among patients recruited from the Mashhad Stroke and Heart Atherosclerotic Disorders (MASHAD) cohort study.

Materials and Methods

Study population

A total of 9761 samples were obtained from individuals recruited to cohort study of MASHAD. This cohort study started in 2007 and will be followed up until 2020. The age of eligible subjects was between 35 and 65 years and participants who had cardiovascular disease were excluded (11). Written consent form was received from all subjects. This recent project was approved by MUMS Ethics Committee.

Study design

We designed two steps in this study: in the first step, cross-sectional study, anti-HSP27 levels of all participants entered to MASHAD study were measured. In the second step, prospective cohort study, we followed up and determine CHD status of MASHAD study population in 2015 to 2016. After that we investigated the association of a genetic variant of the HSPB1-rs2868371 gene locus with CHD. It is necessary to mention that CHD was confirmed by a cardiologist based on the history, previous clinical tests, and other medical examinations.

Demographic data and anthropometric parameters

Demographic data of MASHAD study participants, including: gender, age, and smoking status, physical activity level (PAL), social class including educational and economical levels were collected using a questionnaire. Anthropometric variables including height, BMI, weight, blood pressure, hip and waist circumference, were measured by using standard procedure.

Blood sampling and Biochemical measurements

At baseline a fasted blood sample (after 12 hours fast) was taken from all subjects. Biochemical parameters such as serum total cholesterol (TC), triglycerides (TGs), high density lipoprotein cholesterol (HDL-C), as well as fasting blood glucose (FBG), and serum High-sensitivity C-Reactive Protein (hsCRP) were assessed by using Pars Azmoon kits (mg/ dl) and an Alycon auto analyzer (ABBOTT, Chicago, IL, USA). Low-density lipoprotein cholesterol (LDL-C) level were estimated with Friedewald formula (12) .

Measuring of anti-HSP27 antibody

The in-house method of enzyme-linked immune sorbent assay (ELISA) was used to measure Anti-HSP27 antibodies levels that previously explained in detail (5).

DNA extraction and genotyping

DNA extraction and genotyping were performed in 678 subjects with and without CHD confirmed by cardiologist. DNA extraction was done from blood samples by using YTA Mini-Kit (Yekta Tajhiz Azma, Tehran, Iran). DNA purity and concentration of samples were tested with NanoDrop (NanoDrop-Technologies, Wilmington, USA) .

Genotype analysis of HSPB1-rs2868371 was done by Taqman ®-probes-based assay; PCR reactions were performed in 12.5 ml total volume by using 20 ng of DNA in TaqMan® Universal Master Mix (C-4364338) with specific primers and probes (C-16146175-10; StepOne, Applied Biosystems, USA). We used ABIPRISM-7500 instrument equipped with the SDS version-2.0 software (Foster City, USA) for evaluating the allelic content.

Statistical analysis

The entire statistical analyses were carried out by implementing SPSS version 16.0 (SPSS Inc. Chicago, IL, USA). The normality of data was determined. For comparing parameters between groups, parametric and nonparametric statistical analysis was applied for normal non-normally distributed data respectively. Also, Logistic regression analysis was assessed in order to demonstrate the association between genotypes and event incidence in the presence of confounding variables. The data values were expressed as mean±SD and median (first and third Quartiles) for normally and non-normally distributed data. *P* less than 0.05 were considered as statistically significant.

Results

Clinical specifications of the population

The clinical and baseline characteristics of the population are reported in Table 1. A total of 8776 participants, including 5150 females and 3626 males, were enrolled in the present study. The results indicated that age, physical activity level, waist circumference, blood pressure, FBG, total cholesterol, uric acid, TG, hs-CRP, and smoking status ($P<0.01$ for all factors), as well as BMI and LDL-C ($P<0.05$ for both factors), differed significantly between groups (Table 1). Also, our data revealed that there was no significant difference in anti-HSP27 levels between the study groups ($P>0.05$), although subjects with MI had higher serum anti-HSP27 levels than the stable and unstable angina groups (Table 1).

Association between CAD and anti-HSP27 SNP in follow-up cases

The genetic polymorphism was in Hardy-Weinberg equilibrium ($P>0.05$). The frequency of the CC genotype was 68%, whereas the frequencies of the CG and GG genotypes were 26.8% and 5.2%, respectively, as presented in Table 2. The association of the anti-HSP27 SNP with event prevalence in codominant and dominant genetic models is shown in Table 2. A significant association between the HSP27 genetic variant and the risk of MI in the dominant genetic model was found after adjusting for confounding factors, including sex, age, BMI, physical activity, and smoking; subjects with GG and GC genotypes had a lower risk of MI compared with the reference group (no-event group) [OR=0.27 (95% CI=0.08-0.94), $P=0.040$]. Specifically, subjects with GG and GC genotypes had a lower risk of MI incidence compared with subjects with the C allele (Table 2 and Figure 1).

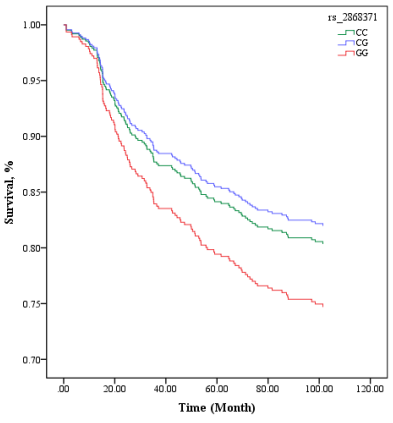

Figure 1. Kaplan Meyer survival curve in subjects with GG and GC genotype which had a lower risk of MI incidence compared to subjects with C allele

Table 1. Baseline Anthropometrics characteristics by event Status, the Mashhad prospective study

		No event (N=8533)	Event (N=235)				*P*
			Stable angina(63)	Unstable angina(118)	MI (27)	Sudden death(27)	
Male; N (%)		3516(97%)	24(0.7%)	57(1.6%)	18(0.5%)	11(0.3%)	0.004
Age (year)		47.87±8.14e	53.68±6.71	54.65±7.38	54.25±6.31	54.73±6.23	<0.001
Physical activity		1.59±0.28b	1.56±0.29	1.50±0.25	1.49±0.31	1.55±0.28	0.007
Waist circumference (cm)		95.04±12.01b	98.68±11.30	99.18±11.10	98.31±8.84	100.37±8.13	<0.001
SBP (mmHg)		121.24±18.00abcd	133.71±23.10	133.96±20.29	133.23±19.14	134.34±21.40	<0.001
DBP (mmHg)		78.96±11.10abd	83.59±10.18	83.50±11.23	82.81±10.21	85.37±11.08	<0.001
FBG (mg/dl)		91.44±36.88abcd	127.13±69.05	113.65±55.65	120.41±67.81	125.77±74.74	<0.001
LDL (mg/dl)		115.88±34.97a	128.17±35.26	117.67±36.83	126.70±	124.55±27.91	0.01
Cholesterol (mg/dl)		190.56±38.57a	204.62±39.09	193.88±40.00	203.00±56.49	211.96±39.49d	<0.001
HDL (mg/dl)		42.81±9.87bc	42.39±8.45	39.66±9.36	37.20±7.75	40.45±9.56	<0.001
Uric acid		4.66±1.40	4.92±1.45	4.98±1.50	5.32±1.38	5.23±2.05	<0.001
BMI (kg/m^2)		27.82±4.70b	28.40±4.48	29.20±4.58	28.79±4.38	28.91±4.66	0.01
TG (mg/dl)		120(87)	135(94)	139(128)	145(137)	164(146)	<0.001
Hs-CRP		1.60(2.45)	2.34(2.28)	1.96(3.77)	1.83(3.70)	2.75(8.45)	<0.001
Anti HSP-27		0.24±0.20	0.23±0.16	0.23±0.19	0.24±0.13	0.25±0.20	0.05>
smoking N (%)	**Non-smoker**	5916(69.3%)	38(60.3%)	75(63.8%)	13(48.1%)	16(59.3)	
	Ex-smoker	828(9.7%)	10(15.9%)	17(14.7%)	8(29.6%)	5(18.5%)	0.006
	Current smoker	1790(21.0%)	15(23.8%)	25(21.6%)	6(22.2%)	6(22.2%)	

Values are expressed as mean±SD, median (IQR) for normally and non-normally distributed variables, respectively. TC: total Cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; FBG: fasting blood glucose, SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high sensitivity- c reactive protein. One way anova, kruskal wallis and chi square test were used.

[a] Association of no event with stable is significant, [b] Association of no event with unstable is significant, [c] Association of no event with MI is significant, [d] Association of no event with sudden death is significant

Table 2. Association of events with Anti-HSP27SNP (Rs2868371)

Anti-HSP27	SNP	Total	No event (%)	Stable angina (%)	Unstable angina (%)	MI (%)	Stable angina vs. No event	Unstable angina vs. No event	MI vs. No event
							Odds ratio (95%CI)	Odds ratio (95%CI)	Odds ratio (95%CI)
codominant	GG	35(5.2%)	26(5%)	5(8.8%)	3(3.9%)	1(4.3%)	2.12(0.74-6.03)	0.67(0.19-2.35)	0.58(0.07-4.62)
	GC	182(26.8%)	143(27.4%)	20(35.1%)	17(29.4%)	2(8.7%)	1.38(0.75-2.54)	0.65(0.36-1.17)	0.21(0.05-0.94)*
	CC	461(68%)	353(67.6%)	32(56.1%)	56(73.7%)	20(87%)	Ref.1	Ref.1	Ref.1
Dominant	GG,GC	217(32%)	169(32.4%)	25(43.9%)	20(26.3%)	3(13%)	1.49(0.84-2.63)	0.65(0.37-1.14)	0.27(0.08-0.94)*
	CC	461(68%)	353(67.6%)	32(56.1%)	56(73.7%)	20(87%)	Ref.1	Ref.1	Ref.1
Recessive	GG	35(5.2%)	26(5%)	5(8.8%)	3 (3.9%)	1(4.3%)	1.89(0.68-5.26)	0.76(0.22-2.61)	0.77(0.09-6.07)
	CC, GC	643(94.8%)	496(95%)	52(91.2%)	73(96.1%)	22(95.7%)	Ref.1	Ref.1	Ref.1
HWE		>0.05	>0.05	>0.05	>0.05	>0.05			
G		251(18.6%)	194(18.6%)	30(26.3%)	23(15.1%)	4(8.7%)	1.55(0.99-2.43)	0.77(0.48-1.24)	0.41 (0.14-1.17)
C		1102(81.4%)	847(81.4%)	84(73.7%)	129(84.9%)	42(91.3%)	Ref.1	Ref.1	Ref.1

The reference category is: No event. Logistic regression analysis adjusted for sex, age, BMI, physical activity, smoking, was used to calculate association of genotype and risk of event incidence. *P<0.05

Discussion

To the best of our knowledge, this was the first study to investigate the relationship between anti-HSP27 levels, a genetic variant in the HSPB1 gene, and CHD events in a large cohort study. The results showed that CAD patients with the GG+GC genotype had a lower risk of developing MI than those with the CC genotype. Also, our data showed a significant difference in serum anti-HSP27 levels between the healthy and CHD study groups. It has been demonstrated that anti-HSP levels are increased in patients with atherosclerosis (11). It has been reported that augmented levels of anti-HSP60/65 and anti-HSP70/72 titers are present in patients with arteriosclerosis and dyslipidemia (13,14) .

Burt *et al*., reported that anti-HSP27 antibody concentrations cannot be considered markers of vascular complications in subjects with type 1 diabetes. They assessed anti-HSP27 antibody levels in 363 type 1 diabetic subjects and compared them with those in 168 healthy individuals in a cross-sectional study. Their results showed that anti-HSP27 titers were the same in type 1 diabetic participants with or without neuropathy complications. Their study included a small sample, and sex was not considered (15). Burut *et al*., measured serum anti-HSP27 levels in 42 glucose-intolerant subjects, with and without a history of CVD (n=21 in each group). They found no significant difference in anti-HSP27 levels between glucose-intolerant subjects with a positive CVD history and those without a CVD history (P=0.06) (16) . Another cross-sectional study was conducted on 63 healthy controls and 60 patients with acute chest pain. Its results showed that although serum anti-Hsp27 levels increased in patients with acute pain, the IgG antibody level to Hsp-27 could not be an independent CVD predictor. This was because these increased anti-Hsp-27 levels were strongly associated with age and hypertension. It is well known that age and diabetes are important predictors of CVD risk (17). Rahsepar *et al*., investigated the association between serum anti-Hsp27 antibody and indices of cardiac function in patients who had undergone coronary artery bypass grafting (CABG) or heart valve replacement. Their study was conducted on 53 coronary patients who underwent off-pump CABG, on-pump CABG, or heart valvular replacement, together with 83 healthy controls. Serum anti-Hsp27 titers were determined 24 h before and after the operation and also at discharge. Their results demonstrated that there is an association between anti-Hsp27 antibody titer and indices of cardiac function in these subjects, so that it was significantly decreased postoperatively and this change was independent of the operative procedure. This observation may be the result of the formation of antigen–antibody immune complexes, and the antibody levels were higher at the time of discharge (18).

A CC genotype (68%) was found at a higher frequency compared with GG (5.2%) and GC (26.8%) genotypes in our population. Moreover, subjects with the GG and GC genotypes, compared with those homozygous for the C allele, had a 27% lower risk of MI. A meta-analysis of three English-language studies and one Chinese study evaluated the association between rs2868371 and the risk of radiation-induced damage in patients with lung cancer. Their results demonstrated that rs2868371 genotypes can be related to radiation-induced esophageal damage risk in Caucasian populations. There was no such association in the Asian population (19) . Xu et al. investigated the relationship between the rs2868371 SNP and survival in American patients (n=224, including 117 males and 107 females) with non-small-cell lung cancer (NSCLC). They reported a significant association between survival and rs2868371 in US patients with NSCLC after radio (chemo) therapy (20). A total of 160 patients with lung cancer who received radiotherapy were recruited in China from September 2009 to December 2011. They found no significant correlation between the rs2868371 genetic polymorphism and the development and progression of radiation-induced lung injury (21). It has been suggested that ethnic differences exist in the distribution of rs2868371 genotypes. Previous studies showed that the CC (20) and CG (22) genotypes are the most common rs2868371 genotypes in American and Chinese populations, respectively. In the current study, the results demonstrated that the CC genotype was more prevalent than the CG and GG genotypes.

In aggregate, our data showed no significant association between anti-HSP27 titers and CHD. Moreover, the results also showed that the CC genotype had a higher frequency than the GG and GC genotypes. No statistically significant differences were found in the frequencies of HSPB1 polymorphisms between healthy and CHD subjects, whereas there was a significantly lower risk of MI in participants with the GG+GC genotype compared with those with the CC genotype. Further studies are required to explore the value of this marker in CAD patients.

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